**RESEARCH PROTOCOL**

Version: 0.0.3

**Use of GLP-1 receptor agonists and subsequent risk of acute liver injury – A self-controlled case series (SCCS) analyses in the OMOP CDM (GLP1-DILI)**

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# Version Control

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| --- | --- | --- |
| **Version** | **Date** | **Changes** |
| 0.0.1 | 29 Sep 2024 | Set up basic document. Added study population, comparators, outcomes. |
| 0.0.2 | 30 Sep 2024 | Edited during first kickoff meeting. Adjusted study population, comparators, outcomes. |
| 0.0.3 | 6 Oct 2024 | Filled out research methods section including rationale/background, design, data sources, population cohort definitions, exposures, outcomes, comparators, data analysis, study diagnostic thresholds. |

# List of Abbreviations

|  |  |  |
| --- | --- | --- |
| **Abbr.** | **Definition** | **Notes** |
| DILI | Drug-Induced Liver Injury |  |
| GLP-1 | Glucagon-Like Peptide-1 |  |
| T2DM | Type 2 Diabetes Mellitus |  |

# Responsible Parties

## Investigators

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## Disclosures

# Abstract

**Background and Significance**

**Study Aims**

**Study Description**

* Population
* Comparators
* Outcomes
* Design
* Timeframe

# Amendments and Updates

# Milestones

# Rationale and Background

Glucagon-like peptide-1 (GLP-1) agonists are a class of medications used to treat type 2 diabetes mellitus (T2DM) and obesity. GLP-1 an endogenous hormone released in response to food consumption, lowering blood glucose through insulin secretion and glucagon inhibition, suppressing appetite, and delaying gastric emptying.

GLP-1 agonists were licensed in the last 20 years for use in overweight patients with T2DM because of benefits with reducing glycated hemoglobin A1c and facilitating weight loss. The US FDA approved the first GLP-1 agonist (exenatide) in 2005.

Currently, the types of GLP-1 agonists that are currently marketed globally are:

Long-acting agonists:

* dulaglutide (Trulicity®)
* exenatide extended-release (Bydureon®)
* liraglutide (Victoza®)
* semaglutide injection (Ozempic®)
* semaglutide tablets (Rybelsus®)

Short-acting agonists:

* exenatide (Byetta®)
* lixisenatide (Adlyxin®)

Clinical trial data, as well as the US FDA Adverse Event Reporting System did not identify a risk of liver enzyme elevation with GLP-1 agonists despite US and Canadian product inserts of liraglutide-containing products lists “elevation of liver enzymes” as an adverse reaction under the Postmarketing Experience section. However, liraglutide-containing products in other countries do not carry any information on the risk of liver enzyme elevation. Likewise, not all GLP-1 agonists labels contain ‘elevation of liver enzymes’ as an adverse reaction as well.

Amidst this uncertainty, some case reports of drug-induced liver injury (DILI) have appeared in the literature. Usage of some of these agents are increasing tremendously following recent findings of randomized trials and market approval for obesity. Understanding the safety profile of GLP-1 agonists is therefore ever more critical.

# Study Objectives

This study aims to evaluate the risk of drug-induced liver injury (DILI) in users of GLP-1 agonists diagnosed with type 2 diabetes mellitus (T2DM) through both a cohort and self-controlled case series (SCCS) methodologies

1. Cohort:
   1. Among patients with T2DM, what is the relative risk of DILI incidence when prescribed GLP-1 agonists compared to other medications?
   2. Among patients with T2DM, what is the relative risk of DILI incidence when prescribed GLP-1 agonists compared to no medication?
2. SCCS: among patients with T2DM and who have been prescribed GLP-1 agonists, what is the relative incidence of developing DILI within an exposure risk period of one year compared to baseline?

# Research Methods

## Study Design

**Cohort Study**

The cohort study will be retrospective cohort of patients with diagnosis of T2DM and who are new users of GLP-1 agonists with two comparator groups (other medication; no medication). The outcome analysed will compare the risk of developing DILI in all three groups.

* Other related T2DM medication will include non-GLP-1 anti-diabetic medications
* Non-medicated groups will include patients with no treatment, or who receive other second-line treatments.

Comparators were chosen based on most commonly occurring medications from LEGEND-T2DM study (https://ohdsi-studies.github.io/LegendT2dm/Protocol).

**SCCS**

Among patients with T2DM and who have been prescribed GLP-1 agonists, what is the relative incidence of developing DILI within an exposure risk period of \_\_ compared to baseline, where baseline can be defined as:

* 1. Periods where no medication is being taken, and/or,
  2. Periods where other medication (as defined in the cohort study) is being taken.

## Data Sources

Both electronic health records (EHR) and claims databases will be analysed. From EHR, we will take lab values based on the definition of DILI. From claims, we will take diagnostic codes.

## Study Population

**Cohort Study**

Inclusion criteria

* All adults (≥18 years) diagnosed with T2DM will be included.

Exclusion criteria

* Pregnant women with history of gestational diabetes (GDM) will be excluded.
* Those with existing history of liver injury prior to taking of GLP-1 agonists will be excluded.
* Those with any history of autoimmune hepatitis as defined by the following criteria will be excluded:
  + Lab test:
  + Abdominal ultrasound
* Those with any history of viral hepatitis as defined by the following criteria will be excluded:

**SCCS**

All adults (≥18 years) diagnosed with T2DM who are taking GLP-1 agonists and have reported cases of DILI will be included.

## Exposures and Comparators

**Cohort Study**

The following medications listed are exposures for the cohort study.

|  |  |  |
| --- | --- | --- |
| **GLP-1 RA** | **Non-GLP-1 RA** | **Other medication** |
| Long-acting agonists:   * dulaglutide (Trulicity®) * exenatide extended-release (Bydureon®) * liraglutide (Victoza®) * semaglutide injection (Ozempic®) * semaglutide tablets (Rybelsus®) | * Empagliflozin (SGLT2 inhibitor) * Sitagliptin (DPP4 inhibitor) * Glipizide (sulfonulurea) | * Insulin * Metformin |
| Short-acting agonists:   * exenatide (Byetta®) * lixisenatide (Adlyxin®) |

Patients must have one year of observation prior to index date and at most 30 days of insulin exposure prior to index date. The cohort will be classified as outlined in the figure below:

A diagram of insulin

Description automatically generated

Patients on other anti-diabetic medications at time of entry into cohort are included as part of a sensitivity analysis.

**SCCS**

Any of the above listed long-acting and short-acting GLP-1 agonists are exposures for the SCCS.

## Outcomes

The outcome is drug-induced liver injury, defined as follows:

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| **Broad definition** | Based on the OHDSI Phenotype Library, the following are classified as broad definitions:   * Acute Hepatic Injury with no pre-existing liver disease * Acute Hepatic Failure in persons with no pre-existing liver disease * All events of Acute Liver Injury, NO viral hepatitis or alcoholic hepatic failure   Based on findings in Athena, the following are also included:   * Chemical and Drug Induced Liver Injury * Chemical and Drug Induced Liver Injury, Chronic * Drug-induced Disorder of Liver * Other injury of liver * Unspecified injury of liver * Injury of liver or gallbladder |
| **Narrow definition** | DILI is a diagnosis of exclusion defined as follows:  **Detailed clinical history**   * Mimicry of acute/chronic liver disease: fever, nausea, vomiting, jaundice, dark urine, itching, RUQ pain * Insufficient information known on histological phenotype for GLP-1 RA DILI, so no differentiation included histologically.   **Liver Biochemistry**   * General DILI biochemistry across all drugs:   + Increased liver enzymes AST, ALT, and/or ALP above a certain threshold (depends on drug) + sometimes raised total bilirubin (TBIL)  |  |  | | --- | --- | | **DILI biochemistry thresholds** | | | Hepatocellular DILI | ALT/AST ≥5-fold above ULN or ratio ≥5 | | Cholestatic DILI | ALP ≥2-fold above ULN or ratio ≤2 | | Mixed DILI | Ratio >2 to <5 |   DILI should be considered if any of the following are met:   * ALT/AST ≥5-fold above ULN * ALP ≥2-fold above ULN * TBIL >2-fold above ULN associated with ALT/AST ≥3-fold above ULN (Hy’s Law)  |  |  | | --- | --- | | **Non-DILI biochemistry ruleouts** | | | Autoimmune-like hepatitis | R factor <20 (if >20, potential for liver injury caused by autoimmune disease) | | Viral panels | (rule out viral hepatitis) | | Antibody panels | (rule out viral hepatitis) | | Drug hypersensitivity | ??? |   **Ruleout Summary**   |  |  | | --- | --- | | **Ruleouts** | | | Autoimmune-like hepatitis | Acute/chronic DILI  Serology/histology idiopathic autoimmune hepatitis | | Liver injury from immune checkpoint inhibitors | Severe acute hepatitis  Histology: granuloma, central endotheliitis, lobular hepatitis | | Drug reaction with eosinophilia and systemic symptoms | Hypersensitivity reaction involving skin + internal organ | | Drug-associated fatty liver disease | Non-alcoholic fatty liver disease attributed to exposure of specific medications | | Acute fatty liver (microvesicular steatosis) | Rapid liver involvement, extensive microvesicular steatosis | | Nodular regenerative hyperplasia | Diffuse nodularity, wide and narrow sheets of hepatocytes at center and periphery respectively, of nodules without advanced fibrosis leading to non-cirrhotic portal hypertension | | Vanishing bile duct (ductopenic) syndrome | Cholestatis + gradual loss of intrahepatic bile ducts | | Secondary sclerosing cholangitis | Acute DILI + histological/features similar to primary sclerosing cholangitis on MRI | | Peliosis hepatis | Randomly distributed blood-filled cavities | | Hepatocellular adenoma/carcinoma | Imaging/histology for adenoma/carcinoma | |

## Covariates

Large-scale propensity score method will be used to adjust for baseline characteristics.

## Negative Controls

**Cohort Study**

To be defined in appendix. Select pairs where no causal effect is expected.

**SCCS**

No negative controls selected

## Analysis Plan

This study will use the Strategus pipeline to call HADES library packages for the following purposes:

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| **Data Characterization** | |
| **Cohort Diagnostics** | Evaluate measurement error in target, comparator, indication, outcome cohorts through CohortDiagnostics package. |
| **Cohort Features** | HADES Characterization and FeatureExtraction – identify patient features in exposure group with outcome vs. no outcome from data prior to observation   * Demographics (age, sex, group, race/ethnicity) * Prior medical history/diagnosis * Prior drug exposures * Prior procedures, measurements, devices, observations * Risk scores |
| **Incidence Rates** | HADES Characterization to calculate (based on intent-to-treat)   * Incidence in GLP-1 RA (#outcomes during GLP1 exposure period/total person days) * Incidence in Non-GLP-1 RA (#outcomes during non-GLP1 exposure period/total person days) * Incidence in Other Medication (#outcomes during other medication exposure period/total person days) |
| **Time-to-Event** | Calculate time to incidence of outcome. |

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| **Cohort Study** | |
| **Comparative Cohort Study** | HADES CohortMethod + Cyclops.   1. Large-scale propensity score to match exposure cohorts with comparators. 2. Sensitivity analysis based on year restriction 3. Cox proportional hazards to estimate risk of DILI via ITT 4. Residual bias via negative controls |

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| --- | --- |
| **Self-Controlled Case-Series** | |
| **SCCS** | HADES SelfControlledCaseSeries + Cyclops   1. Relative incidence of DILI |

# Study Diagnostic Thresholds

1. PS distribution
2. Patient characteristics table before/after PS adjustment
3. Negative control calibration plot for RB
4. Kaplan-Meier plots for Cox

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| --- | --- |
| **Cohort Study** | |
| **Covariate Balance (SMD)** | <0.1 |
| **Empirical Equipoise (PS)** | >0.1 |
| **Residual Bias (EASE)** | <0.25 |
| **Meta-analysis Heterogeneity** | <0.4 |
| **Meta-analysis MDRR** | <10 |

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| **Self-Controlled Case-Series** | |
| **Pre-exposure** | >0.05 |
| **Time Trend** | >0.05 |
| **EASE** | <0.25 |
| **Meta-analysis Heterogeneity** | <0.4 |
| **Meta-analysis MDRR** | <10 |

# Strengths and Limitations

# Protection of Human Subjects

Participating institutions should seek IRB approval for this study as necessary.

# Plans for Disseminating and Communicating Study Results

Results will be shared/discussed during the OHDSI APAC Symposium if sufficient data has been gathered. This work will be presented at conferences and published as a manuscript.

# Appendix

## Cohort Definitions

## Negative Controls

# References

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